PALLIATION OF OPIOID-INDUCED CONSTIPATION: WHAT’S NEW

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OBJECTIVES

• Review prevalence and impact of opioid-induced constipation (OIC)

• Discuss the available treatment options for OIC with an emphasis on pathophysiology

• Devise a therapeutic plan to incorporate new pharmacologic agents for refractory constipation

DEFINITIONS

• Opioid-Induced Constipation (OIC)

• Opioid-Induced Bowel Dysfunction (OIBD)
  > motility
  > coordination of sphincter function
  > coordination of secretion

OIB/OIC PREVALENCE & IMPACT

** Lack of uniform definition, interpret with caution **

• OIC probably most well characterized adverse event in opioid-treated patients

• Multinational, internet-based survey of 322 chronic opioid users: 81% despite use of laxatives

• Larger, population-based survey of 2055 pts on opioids + laxatives for chronic non-cancer pain: 57% prevalence of constipation

CASE

• 46yo WF with PMH significant for stage V breast cancer, left sided malignant pleural effusion s/p-PleurX catheter presenting with shortness of breath. Medicine team consult for pharmacy pain evaluation due to high dose opioid analgesics and non-formulary Relistor

  • Morphine SA 300mg po q8h
  • Hydromorphone 16mg po q4h prn
  • Metoclopramide 10mg po tid
  • Docusate 100mg po bid
  • Senna 17.2mg po bid
  • Polyethylene glycol 17grams po bid
  • Methylhathiononate/Relistor 12mg/0.6ml SubQ q48h

TOWARDS A CONSENSUS DEFINITION OF OIC

A change when initiating opioid therapy from baseline bowel habits that is characterized by any of the following:

• Reduced bowel movement frequency

• Development or worsening of straining to pass bowel movements

• Sense of incomplete rectal evacuation

• Harder stool consistency
ASSESSMENT TOOLS

- Bowel Function Index (BFI)
- Patient Assessment of Constipation-Symptoms
- Bristol Stool Chart
- Electronic Bowel Function Diary

1. Morlion B et al. 2015.

PATHOPHYSIOLOGY

- 3 types of opioid receptors involved in controlling normal GI function
  - Mu, Delta, Kappa
- Endogenous and exogenous opioids activate Mu receptors
  - Ultimately inhibit conversion of ATP to cAMP, reduce cellular functions
- Opioids also directly activate K+ channels and inhibit Ca2+
  - Net result = reduced release of neurotransmitters, decreased neuronal activity


PATHOPHYSIOLOGY DRIVING TREATMENT

1. Dryer, harder stool
2. Feeling of incomplete evacuation
3. Reduced propulsive peristalsis

1. Holzer P. 2004
2. Holzer P. 2009

TREATMENT

- Currently, laxatives are primary treatment of OIBD
- Previously approved peripherally acting mu opioid receptor antagonists (PAMORAs)
  - Methylaltrexone (Relistor)
  - Alvimopan (Entereg)

1. Dryer K et al. 2014
2. Siemens W et al. 2015

- Newer agents
  - Lubipristone (Artizel)
  - Natuxegel (Movantik)
  - TD-1211 (Asetopran)
  - Naloxone Sustained Release

1. Coyne KS et al. 2014
3. Merck & Co Inc. 2015

LET'S NOT FORGET....

- Many patients have inadequate traditional bowel regimens
  - Docusate, senna/bisacodyl, lactulose, sorbitol, polyethylene glycol, steroids(obstruction), prune juice, various enemas and suppositories, manual dis-impaction, digital rectal stimulation...
- Failure of “prn” bowel regimens does not necessitate escalation to new, costly agents

LEADERS IN...
NEWER AGENTS

Lubiprostone (Amitiza)

- **MOA**: Chloride channel activator
- **FDA Indications**: CIC (2006), IBS (2008)
- **Dosing**: 24mcg PO BID with food and water
  - **Pearls from Clinical Studies**:
    - Significant increase in spontaneous bowel movements (SBMs/week compared to placebo)
    - Median time to 1st BM 28.5h (not different than placebo)
    - Long-term efficacy over 9 months found inc’d number of SBMs/week from 1.4 at baseline to 4.9
    - Not superior to placebo in reliance on rescue therapy w/ laxative
    - Improvements in OIBD symptoms noted (straining, severity of constipation, bloating)

FDA Indications
- OIC (2013)

Dosing
- 24mcg PO BID with food and water
- Dose adjusted for hepatic impairment
- Not superior to placebo in reliance on rescue therapy w/ laxative
- Improvements in OIBD symptoms noted (straining, severity of constipation, bloating)

ON THE HORIZON

Naloxegol (Movantik)

- **MOA**: Pegylated naloxone derivative
- **FDA Indications**: CIC in CNCP (2014)
- **Dosing**: 25mg po daily, empty stomach
  - Reduce to 12.5mg for:
    - Intolerance
    - CrCl less than 60ml/min
  - Co-administered with moderate CYP3A4 inhibitors
- **Pearls from Clinical Studies**:
  - KODIAC 04, KODIAC 05
  - Statistically significant improvements in straining, stool consistency, and complete spontaneous bowel movement (SBM)
  - 12.5mg achieved significantly greater response than placebo in KODIAC 04 only
  - 25mg dose reached statistical significance in both studies
  - 25mg dose resulted in shorter median time to first SBM
  - No significant difference in bioavailability or between treatment arms

ON THE HORIZON

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TD-1211 (Axelopran)

- **MOA**: PAMORA
- **FDA Indications**: Not yet approved
- **Dosing**: No formal recommendation, but has been studied most recently at 5mg, 10mg, 15mg orally
- **Pearls from Clinical Studies**:
  - Efficacy evaluated in three phase 2 studies
  - Definitions of OIC, spontaneous bowel movement (SBM) or complete SBM were not provided
  - Doses of 5 and 10mg produced greatest SBMs/week
  - Median time to first SBM 8.6hrs (5mg) and 3.6hrs (10mg) compared to 28.7hrs (placebo)
  - Studies reported no clinically significant changes in lab tests, ECG, or vital signs but did not report the data

ON THE HORIZON

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Sustained Release Naloxone (NSR)

- **MOA**: Modified release reduces systemic concentrations, acts like a PAMORA
- **FDA Indications**: Not approved as single agent
- **Dosing**: 2.5mg/day - 40mg/day orally
- **Pearls from Clinical Studies**:
  - 40 patients randomized in blocks to receive 2.5mg, 5mg, 10mg or 20mg
  - 6 week study, doses inc’d to BID at week 4
  - At week 3, mean change in SBMs/week was statistically significant compared to placebo for only 20mg
  - At week 6, only 10mg BID dose achieved statistical significance compared to placebo
  - Opioid withdrawal: no statistically significant change from baseline or compared to placebo

Case Revisited

- 46yo WF with PMH significant for stage V breast cancer
- Last BM 4 days prior
- Normal: BM every other day, bristol stool type 2, endorses moderate straining with each BM, frequent feeling of incomplete evacuation

- **Scenario 1**
  - Continue current bowel regimen, including methylnaltrexone 12mg SubQ q48hr
  - Add docusate mini enema (Enemeez), 2 enema NOW PR then q48hr

- **Scenario 2**
  - Discontinue methylnaltrexone, continue docusate, senna, polyethylene glycol
  - Add enema or suppository “NOW” dose

Clinical Pearls

- Safe to assume opiates/opioids constipate everyone
- Bowel regularity assessment should include discussion beyond frequency
- Pathophysiology of OIC/OIBD often results in dry/hard stools, incomplete evacuation, and reduced propulsive peristalsis
- Newer agents do not replace standard of care
- Many agents were only studied against placebo
- Rescue laxatives were required in most clinical studies
REFERENCES


2016 ANNUAL MEETING

REFERENCES

• Axelopran (TD-1211) briefing document: Anesthetic and Analgesic Drug Products Advisory Committee of 2014 Jun 11-12.
• Axelopran (TD-1211) briefing document: Anesthetic and Analgesic Drug Products Advisory Committee of 2014 Jun 11-12.